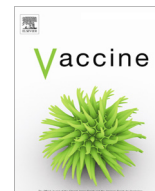




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# Effectiveness of Covid-19 vaccines against symptomatic and asymptomatic SARS-CoV-2 infections in an urgent care setting

Madhura S. Rane<sup>a,\*</sup>, McKaylee M. Robertson<sup>a</sup>, Sarah G. Kulkarni<sup>a</sup>, Daniel Frogel<sup>b</sup>, Chris Gainus<sup>b</sup>, Denis Nash<sup>a,c</sup>

<sup>a</sup> Institute for Implementation Science in Population Health, City University of New York, New York, NY, USA

<sup>b</sup> CityMD/Summit Medical Group, New York, NY, USA

<sup>c</sup> Department of Epidemiology and Biostatistics, Graduate School of Public Health and Health Policy, City University of New York, New York, NY USA



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## ABSTRACT

**Background:** It is critical to monitor changes in vaccine effectiveness against COVID-19 outcomes for various vaccine products in different population subgroups.

**Methods:** We conducted a retrospective study in patients  $\geq 12$  years who underwent testing for SARS-CoV-2 virus from April 14 through October 25, 2021, at urgent care centers in the New York metropolitan area. Patients self-reported vaccination status at the time of testing. We used a test-negative design to estimate vaccine effectiveness (VE) by comparing odds of a positive test for SARS-CoV-2 infection among vaccinated ( $n = 474,805$ ), partially vaccinated ( $n = 87,834$ ), and unvaccinated ( $n = 369,333$ ) patients, adjusted for demographic factors and calendar time.

**Results:** VE against symptomatic infection after 2 doses of mRNA vaccine was 96% (95% Confidence Interval: 95%, 97%) in the pre-delta period and reduced to 79% (95% CI: 77%, 81%) in the delta period. In the delta period, VE for 12–15-year-olds (85%; [95% CI: 81%, 88%]) was higher compared to older age groups (<65% for all other age groups). VE estimates did not differ by sex and race/ethnicity. VE against symptomatic infection was the highest for individuals with a prior infection followed by full vaccination. VE against symptomatic infection after the 2-dose mRNA-1273 vaccine (82% [95% CI: 80%, 84%]) was higher compared to the BNT162b2 vaccine (76% [95% CI: 74%, 78%]) in the delta period. VE after 1-dose of the Ad26.COV2.S vaccine was the lowest compared to other vaccines (19% [95% CI: 15%, 23%]) in the delta period.

**Conclusions:** VE against infection after two doses of the mRNA vaccines was high initially, but significantly reduced against the delta variant for both FDA-approved vaccines.

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## 1. Introduction

As of November 2022, the COVID-19 pandemic has claimed 6.6 million lives globally, with over a million deaths reported in the United States (US) [1]. Vaccines remain the most effective public health tool against COVID-19 morbidity and mortality. In the US, the Pfizer-BioNTech BNT162b2 [2] and the Moderna mRNA-1273 vaccines [3] have received full approval from the U.S. Food and Drug Administration (FDA) for both primary and booster doses [4], while the Janssen Ad26.COV2.S vaccine [5] and the Novavax

protein subunit vaccine [6] are currently authorized for emergency use for adults over 18. The FDA has also authorized Pfizer-BioNTech and Moderna vaccines for children 6 months–17 years old for emergency use [7]. All recommended vaccines have shown high efficacy against severe disease and mortality in clinical trials against the alpha and delta variants of SARS-CoV-2 virus [3,5,6,8]. Boosting with mRNA vaccines was moderately effective against the highly transmissible B.1.1.529 (Omicron) variant which became predominant in November 2021 [9–12]. However, there is evidence of waning vaccine protection against infection and severe disease [13–16].

Few studies have compared effectiveness of authorized vaccines against different variants in the same study population, which is also demographically diverse [17]. Evidence on whether vaccination after prior infection (hybrid immunity) protects better against

**Abbreviations:** VE, vaccine effectiveness; PCR, polymerase chain reaction; FDA, Food and Drug Administration; EMR, Electronic Medical Records; OR, Odds Ratio.

\* Corresponding author at: CUNY Graduate School of Public Health and Health Policy, 55 W. 125th St., 6th Floor, New York, NY 10027, USA.

E-mail address: [madhura.rane@sph.cuny.edu](mailto:madhura.rane@sph.cuny.edu) (M.S. Rane).

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reinfection is also scarce [18]. In this study, we used a test-negative case-control design [19], comparing vaccination history among people who test positive (cases) and negative (controls), to estimate vaccine effectiveness (VE) against symptomatic and asymptomatic SARS-CoV-2 infection over time in a population of patients seeking care at CityMD, a large ambulatory care center in NYC and neighboring areas. We also compared vaccine-induced, infection-induced, and hybrid protection against SARS-CoV-2 infection by vaccine product.

## 2. Methods

### 2.1. Study population, setting, and design

We conducted a test-negative case control study to estimate vaccine effectiveness of different COVID-19 vaccines among residents of New York City and surrounding metropolitan area who received a polymerase chain reaction (PCR) test or a rapid antigen test for SARS-CoV-2 at one of the 115 CityMD New York locations in the five boroughs of NYC (n = 76), Long Island, NY (n = 32), and Westchester, NY (n = 7).

CityMD started entering vaccination data in their EMR in March 2021. We only included COVID-19 diagnostic tests occurring at least 14 days after the COVID-19 vaccine eligibility date for different age groups in NYC. Specifically, individuals  $\geq 30$  years of age who received at least one PCR or antigen test at CityMD clinics after April 15, 2021, those between 16 and 29 years of age who received a test after April 20, 2021 and those between 12 and 15 years of age who received a test after May 27, 2021 were included in the study [20,21]. Study ended on October 25, 2021. We excluded individuals  $<12$  years and those with missing vaccination status. Only the first positive test for each patient was included. Negative tests performed within 7 days of a previous negative test and within 21 days of a positive test result were excluded, since they could be associated with the same illness [22] or be false negatives.

This study was approved by the Institutional Review Board of the City University of New York. Patient consent was not obtained because deidentified electronic health records were used.

### 2.2. Exposure and outcome measures

**COVID-19 vaccination:** Data on COVID-19 vaccination status was systematically ascertained via patient self-report as part of their intake and history. At the time of testing, patients reported whether they received a COVID-19 vaccine, the vaccine manufacturer, and whether two weeks have elapsed since their final dose. Patients who reported receiving only one dose of the mRNA vaccines or 2 doses within 2 weeks of the day of testing were defined as partially vaccinated. Those receiving 2 doses of the mRNA vaccine at least 2 weeks before testing were defined as fully-vaccinated.

**SARS-CoV-2 infection - Cases and Controls:** Testing for SARS-CoV-2 conducted at CityMD using assays authorized by the FDA, included: PCR tests of respiratory tract specimens for SARS-CoV-2 RNA collected via nasopharyngeal and nasal swabs and rapid antigen tests of respiratory tract specimens collected via anterior nasal swabs. All patients were evaluated by a licensed clinician.

**Symptomatic and Asymptomatic SARS-CoV-2 Infection:** We defined symptomatic COVID-19 as SARS-CoV-2 positive patients who exhibited at least one of these symptoms: fever, oxygen saturation  $< 95\%$ , chills, cough, headache, fatigue, myalgia, sore throat, chest tightness, shortness of breath, loss of sense of taste and smell, nausea, vomiting, diarrhea, chest pain, confusion/altered mental state as recorded in the CityMD Electronic Medical Records (EMR) using ICD-10 codes. If no symptoms were recorded,

patients were considered asymptomatic. Date of visit was used as a proxy for the date of symptom onset.

**Covariates:** Patient age, sex, race/ethnicity, comorbidities, region of residence, no. of tests performed at CityMD prior to April 15, 2021, and BMI were obtained from the EMR. We assumed that the absence of information on comorbidities, symptoms, and previous tests in the EMR meant that none were present.

**Statistical analysis:** Chi-squared test was used to compare characteristics between test positive cases and test negative controls and between vaccinated and unvaccinated testers. Multivariable logistic regression was used to estimate the odds ratio (OR) of vaccination comparing cases and controls. VE was calculated as  $(1 - \text{OR}) \times 100\%$ . ORs were adjusted for the covariates listed above, selected *a priori* as potential confounders. To account for temporal confounding due to increasing vaccine coverage, different timing of vaccine eligibility for different age groups, and changing SARS-CoV-2 incidence over time, we adjusted the models for calendar time grouped in 2-week intervals.

**Vaccine effectiveness for mRNA vaccines:** For the main analysis, we estimated VE for two-dose mRNA vaccines combined. Patients who received the one-dose Janssen vaccine (6% of the study sample) were excluded. Patients tested positive at any time prior to April 15, 2021, by PCR, rapid test, or antibody tests conducted at CityMD clinics were excluded from the analysis to measure vaccine effectiveness of mRNA vaccines. For all models, VE before the delta variant became predominant in the NYC area (April 15, 2021 - June 10, 2021, henceforth referred to as 'pre-delta period') and during delta variant predominance (June 11, 2021 - October 25, 2021, 'delta period') were compared. VE was also estimated stratified by age group (12–15 years, 16–30 years, 31–50 years, 51–64 years 65–80 years,  $>80$  years), sex, presence of comorbidities, and race/ethnicity.

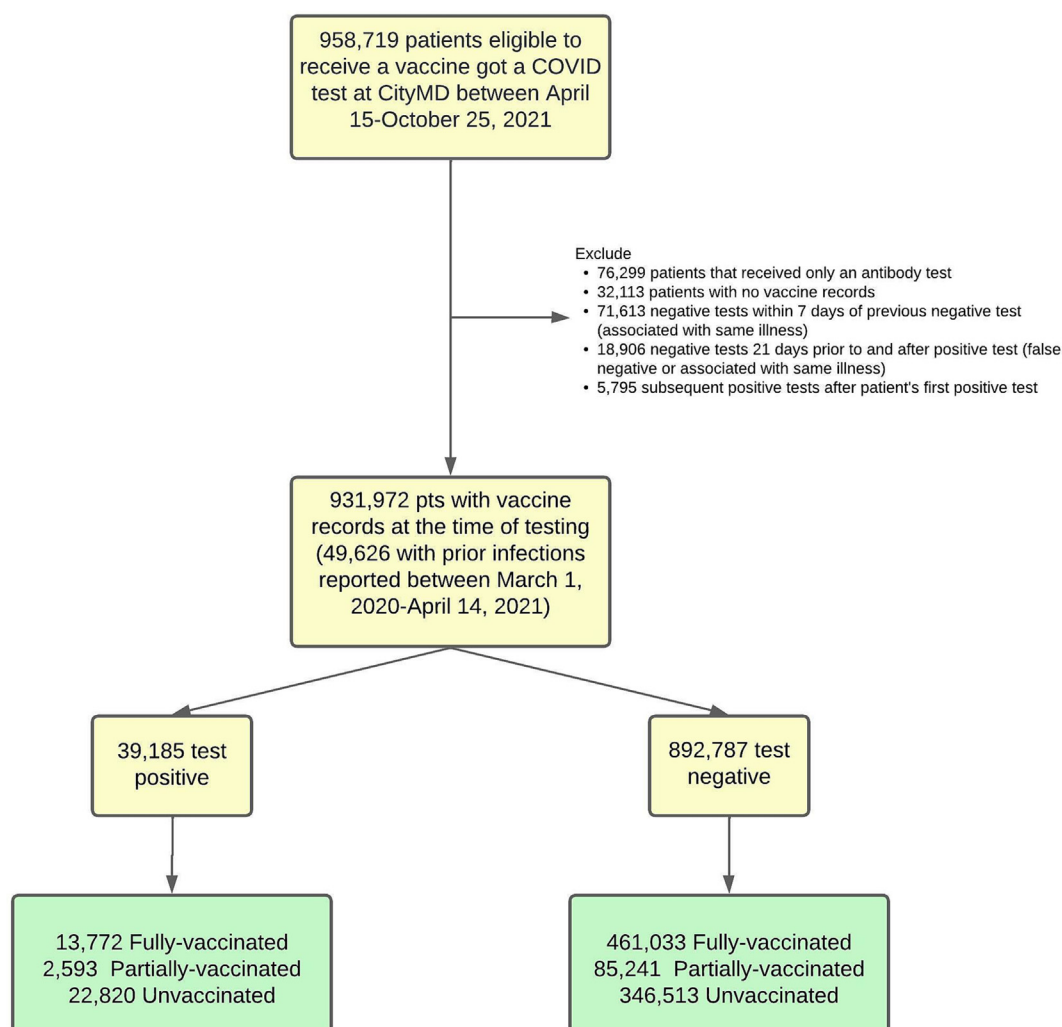
### 2.3. Vaccine-induced and infection-induced protection by vaccine product

We compared vaccine-induced and infection-induced protection separately for each vaccine product (Pfizer-BioNTech BNT162b2, Moderna mRNA-1273, and Janssen Ad26.COV2.S), adjusted for the same covariates above. In this analysis, patients with prior infections diagnosed at CityMD between March 1, 2020 and April 15, 2021 were included. Patients with no vaccine-induced or infection-induced protection (reference group) were compared to patients with a previous infection but no vaccine (infection-induced protection only), previous infection + one or two doses of vaccine (hybrid protection), and one or two doses of vaccine but no previous infection (vaccine-induced protection only).

As a sensitivity analysis to assess whether the type of test used (RT-PCR vs. rapid antigen test) biased VE estimates, we estimated VE for 2-dose mRNA vaccines against any infection restricted to patients who received only the RT-PCR test. All analyses were conducted in R 4.0.1 (Vienna, Austria). Tests were two-sided with P-value  $< 0.05$  considered significant.

## 3. Results

The study sample included 958,719 individuals who contributed at least one COVID-19 RT-PCR (n = 657,450 tests) or rapid antigen test (n = 721,124 tests) between April 15, 2021, and October 25, 2021 (Fig. 1). The median age of study participants was 33 years (interquartile range, 25–49). Patient characteristics by vaccination and SARS-CoV-2 infection status are described in Table 1. A total of 39,185 (4.2%) patients tested positive at least once for the SARS-CoV-2 virus, while 50.9% were fully-vaccinated, 9.4% were partially vaccinated, and 39.6% were unvaccinated at the time of testing. Among positive individuals, 14.1%



**Fig. 1.** Flow chart of study participants tested for SARS-CoV-2 between April 1, 2021 and October 25, 2021 at CityMD clinics in New York City and surrounding metropolitan area.

were symptomatic at the time of testing. Fully-vaccinated individuals were more likely to be tested multiple times before study started compared to unvaccinated individuals (27.9% vs. 17.8%), and were more likely to report having chronic diseases (20.8% vs. 17.1%), depression/anxiety (7.5% vs. 3.2%), and immunocompromised disease (1.2%, 0.5%). The proportion of testers vaccinated at the time of testing increased over time from 37.7% in April 2021 to 70.8% in October 2021 ([Supplementary Fig. 1](#)).

### 3.1. Vaccine effectiveness over time

Vaccine effectiveness (VE) against any SARS-CoV-2 infection (symptomatic or asymptomatic) after 2 doses of mRNA vaccines (BioNTech BNT162b and mRNA-1273 combined) decreased with calendar time. Adjusted VE after 2 doses of mRNA vaccines was high (87% [95% CI: 85%, 89%]) in April 2021. By mid-June 2021, VE dropped to 69% (95% CI: 62%, 74%), and by October 2021, declined further to 54% (95% CI: 44%, 62%) ([Fig. 2](#)).

### 3.2. Vaccine effectiveness by variant period and subgroups

Overall, adjusted VE against symptomatic infection was 96% (95% CI: 95%, 97%) in the pre-delta period and reduced to 79% (95% CI: 77%, 81%) in the delta period. When symptoms were

restricted to high fever ( $>101.4$  deg) or  $O_2 < 95\%$ , VE against symptomatic infection increased slightly to 83% (95% CI: 81%, 85%) in the delta period. VE against asymptomatic infection was lower than symptomatic infection (85% [95% CI: 84%, 86%] in the pre-delta period and 58% [95% CI: 57%, 59%] in the delta period ([Fig. 3](#)).

Adjusted VE with 2-dose mRNA vaccines against any infection was higher in the pre-delta compared to delta period for all demographic subgroups. VE for ages 16 to 64 years was  $>85\%$  in the pre-delta period vs.  $<65\%$  in delta period. VE was lower for 64+ year olds compared with  $<64$  year olds, even in the pre-delta period. Compared to age groups older than 16 years, higher VE was observed for 12–15 year olds (85%; [95% CI: 81%, 88%]) in the delta period. Patients with chronic diseases (59%; [95% CI: 57%, 62%]), depression/anxiety (54%; [95% CI: 48%, 60%]) and immunosuppressive diseases (58%; [95% CI: 43%, 69%]) had lower VE compared to those with no comorbidities (63%; [95% CI: 62%, 64%]) in the delta period. VE estimates were comparable across sex and race/ethnicity both pre-delta and delta period ([Fig. 3](#)).

### 3.3. Comparison between vaccine-induced and infection-induced protection, by vaccine product

A total of 49,626 participants had previous infections documented between March 1, 2020 and April 14, 2021 (average time

**Table 1**

Characteristics of participants tested for SARS-CoV-2 between April 15, 2021, and October 25, 2021, at CityMD clinics in New York City and surrounding metropolitan area.

Characteristics	Vaccination status			P-value	SARS-CoV2 Test status		
	Fully (N = 474805)	Partial <sup>a</sup> (N = 87834)	Unvaccinated (N = 369333)		Test Positive (N = 39185)	Test Negative (N = 892787)	P-value
<i>COVID-19 positive</i>							
Test Positive	13,772 (2.9%)	2593 (3.0%)	22,820 (6.2%)	<0.001	–	–	–
Test Negative	461,033 (97.1%)	85,241 (97.0%)	346,513 (93.8%)		–	–	–
<i>Vaccination status</i>							
Fully	–	–	–	–	13,772 (35.1%)	461,033 (51.6%)	<0.001
Partial	–	–	–	–	2593 (6.6%)	85,241 (9.5%)	
Unvaccinated	–	–	–	–	22,820 (58.2%)	346,513 (38.8%)	
<i>Age</i>							
12–18	21,503 (4.5%)	8611 (9.8%)	42,741 (11.6%)	<0.001	2500 (6.4%)	70,355 (7.9%)	<0.001
19–29	143,521 (30.2%)	26,091 (29.7%)	113,937 (30.8%)		13,340 (34.0%)	270,209 (30.3%)	
30–39	105,214 (22.2%)	18,830 (21.4%)	89,286 (24.2%)		9941 (25.4%)	203,389 (22.8%)	
40–49	66,309 (14.0%)	13,178 (15.0%)	54,134 (14.7%)		5562 (14.2%)	128,059 (14.3%)	
50–59	63,119 (13.3%)	11,531 (13.1%)	40,608 (11.0%)		4179 (10.7%)	111,079 (12.4%)	
60–69	46,518 (9.8%)	6316 (7.2%)	19,880 (5.4%)		2352 (6.0%)	70,362 (7.9%)	
70–79	21,919 (4.6%)	2468 (2.8%)	6755 (1.8%)		964 (2.5%)	30,178 (3.4%)	
>=80	6702 (1.4%)	809 (0.9%)	1992 (0.5%)		347 (0.9%)	9156 (1.0%)	
<i>Sex</i>							
Male	197,969 (41.7%)	37,714 (42.9%)	156,326 (42.3%)	<0.001	18,582 (47.4%)	373,427 (41.8%)	<0.001
Female	276,756 (58.3%)	50,111 (57.1%)	212,971 (57.7%)		20,595 (52.6%)	519,243 (58.2%)	
Unknown	80 (0.0%)	9 (0.0%)	36 (0.0%)		8 (0.0%)	117 (0.0%)	
<i>Race/Ethnicity</i>							
White NH	192,843 (40.6%)	26,288 (29.9%)	81,094 (22.0%)	<0.001	12,902 (32.9%)	287,323 (32.2%)	<0.001
Black NH	47,476 (10.0%)	11,694 (13.3%)	82,998 (22.5%)		6322 (16.1%)	135,846 (15.2%)	
Hispanic	101,246 (21.3%)	25,550 (29.1%)	120,163 (32.5%)		10,509 (26.8%)	236,450 (26.5%)	
Nat Am./Pac Is./Al Nat.	2675 (0.6%)	601 (0.7%)	2777 (0.8%)		256 (0.7%)	5797 (0.6%)	
Asian	51,999 (11.0%)	8185 (9.3%)	12,782 (3.5%)		2414 (6.2%)	70,552 (7.9%)	
Other/Unknown	78,566 (16.5%)	15,516 (17.7%)	69,519 (18.8%)		6782 (17.3%)	156,819 (17.6%)	
<i>Region</i>							
Bronx	43,652 (9.2%)	10,816 (12.3%)	65,650 (17.8%)	<0.001	5012 (12.8%)	115,106 (12.9%)	<0.001
Brooklyn	94,335 (19.9%)	15,015 (17.1%)	75,789 (20.5%)		8166 (20.8%)	176,973 (19.8%)	
Manhattan	147,531 (31.1%)	23,254 (26.5%)	47,404 (12.8%)		7647 (19.5%)	210,542 (23.6%)	
Queens	61,105 (12.9%)	12,480 (14.2%)	52,021 (14.1%)		5365 (13.7%)	120,241 (13.5%)	
Staten Island	11,358 (2.4%)	2008 (2.3%)	15,280 (4.1%)		1881 (4.8%)	26,765 (3.0%)	
Long Island	77,947 (16.4%)	17,556 (20.0%)	89,884 (24.3%)		8089 (20.6%)	177,298 (19.9%)	
Westchester	38,877 (8.2%)	6705 (7.6%)	23,305 (6.3%)		3025 (7.7%)	65,862 (7.4%)	
<i>Symptomatic at testing (reported)</i>							
Symptomatic <sup>*</sup>	60,739 (12.8%)	8500 (9.7%)	35,857 (9.7%)	<0.001	5526 (14.1%)	99,570 (11.2%)	<0.001
No symptoms reported	422,748 (87.3%)	97,472 (90.6%)	422,970 (90.7%)		33,659 (85.9%)	793,217 (88.8%)	
High fever or O2 < 95	8155 (1.7%)	1471 (1.7%)	6533 (1.8%)		2747 (7.0%)	13,412 (1.5%)	
<i>Previous COVID infection</i>							
Yes	22,890 (4.8%)	4648 (5.3%)	22,088 (6.0%)	<0.001	244 (0.6%)	49,382 (5.5%)	<0.001
No	451,915 (95.2%)	83,186 (94.7%)	347,245 (94.0%)		38,941 (99.4%)	843,405 (94.5%)	
<i>No. of tests prior to study start period<sup>*</sup></i>							
0	240,914 (50.7%)	50,918 (58.0%)	226,908 (61.4%)	<0.001	24,309 (62.0%)	494,431 (55.4%)	<0.001
1	101,604 (21.4%)	17,586 (20.0%)	76,600 (20.7%)		7760 (19.8%)	188,030 (21.1%)	
>=2	132,287 (27.9%)	19,330 (22.0%)	65,825 (17.8%)		7116 (18.2%)	210,326 (23.6%)	
<i>Symptomatic at rapid testing<sup>+</sup></i>							
Yes	163,975 (34.5%)	22,925 (26.1%)	96,867 (26.2%)	<0.001	28,875 (73.7%)	254,892 (28.6%)	<0.001
No	260,378 (54.8%)	54,018 (61.5%)	229,992 (62.3%)		8913 (22.7%)	535,475 (60.0%)	
Missing	50,452 (10.6%)	10,891 (12.4%)	42,474 (11.5%)		1397 (3.6%)	102,420 (11.5%)	



Table 1 (continued)

Characteristics	Vaccination status		SARS-CoV2 Test status			
	Fully (N = 474805)	Partial <sup>§</sup> (N = 87834)	Unvaccinated (N = 369333)	P-value	Test Positive (N = 39185)	Test Negative (N = 892787)
<b>Comorbidities</b>						
Depression/anxiety	35,386 (7.5%)	4224 (4.8%)	11,654 (3.2%)	<0.001	1672 (4.3%)	49,592 (5.6%)
Immunocompromising diseases	5512 (1.2%)	518 (0.6%)	1979 (0.5%)	<0.001	289 (0.7%)	7720 (0.9%)
Chronic diseases	98,951 (20.8%)	15,042 (17.1%)	59,584 (16.1%)	<0.001	6571 (16.8%)	167,006 (18.7%)
<b>BMI</b>						
Healthy	184,300 (38.8%)	30,791 (35.1%)	108,342 (29.3%)	<0.001	13,597 (34.7%)	309,836 (34.7%)
Obese	90,994 (19.2%)	18,128 (20.6%)	93,269 (25.3%)		9047 (23.1%)	193,344 (21.7%)
Overweight	129,843 (27.3%)	23,875 (27.2%)	102,062 (27.6%)		11,453 (29.2%)	244,327 (27.4%)
Underweight	11,286 (2.4%)	2365 (2.7%)	8864 (2.4%)		825 (2.1%)	21,690 (2.4%)
Missing	58,382 (12.3%)	12,675 (14.4%)	56,796 (15.4%)		4263 (10.9%)	123,590 (13.8%)

NH: Non-Hispanic; Nat Am./Pac Is./Al Nat.: Native American/Pacific Islander/Alaskan Native; BMI: Body Mass Index.

Column percentages used.

<sup>a</sup> Symptomatic case defined as patients with at least one of these symptoms: fever, oxygen saturation <95%, chills, cough, headache, fatigue, myalgia, sore throat, chest tightness, shortness of breath, loss of sense of taste and smell, nausea, vomiting, diarrhea, chest pain, confusion/alter mental state. For patients with rapid tests, presence of symptoms was also recorded in the EMR as a binary variable (Yes/No) by physicians.

<sup>b</sup> Chronic comorbidities included history of hypertension, heart disease, high cholesterol, asthma, chronic obstructive pulmonary disease, diabetes, and kidney disease. Immunocompromising diseases include cancer and HIV.

<sup>c</sup> Prior tests were counted between March 1, 2020 and April 15, 2021. Number of prior tests could represent multiple factors such as health care utilization, exposure risk, or employment-related testing.

<sup>d</sup> For those who received only 1 dose of the 2-dose mRNA vaccines (partially vaccinated), it is not known if the dose was given 2 weeks prior to when diagnostic test was conducted.

between prior infection and second infection during study period: 123.9 days, range: 46–589 days). Protection against symptomatic infection was the highest for those fully-vaccinated by any of the vaccines and had a history of infection (Fig. 4a, b, c). Compared to those unvaccinated with no prior infections, those unvaccinated **with** prior infections had a 91% (95% CI: 82%, 95%) reduction in odds of symptomatic infection in the pre-delta period and 91% (95% CI: 86%, 94%) reduction in odds in the delta period (Fig. 4).

Among those **without** documented prior infection, VE against symptomatic infection after 2 doses of the BNT162b2 vaccine was 96% (95% CI: 94%, 97%) in the pre-delta period and declined to 76% (95% CI: 74%, 78%) in the delta period (Fig. 4a). VE after 2 doses of the mRNA-1273 vaccine against symptomatic infection was higher compared to the BNT162b2 vaccine (82% [95% CI: 80%, 84%]) in the delta period (Fig. 4b). VE after 1 dose of the Ad26.COV2.S vaccine was much lower compared to the 2-dose mRNA vaccines (46% [95% CI: 39%, 52%] in the pre-delta period and 19% [95% CI: 15%, 23%] in the delta period) (Fig. 4c). mRNA-1273 vaccine had higher VE against asymptomatic diseases compared to the BNT162b2 vaccine (Fig. 5).

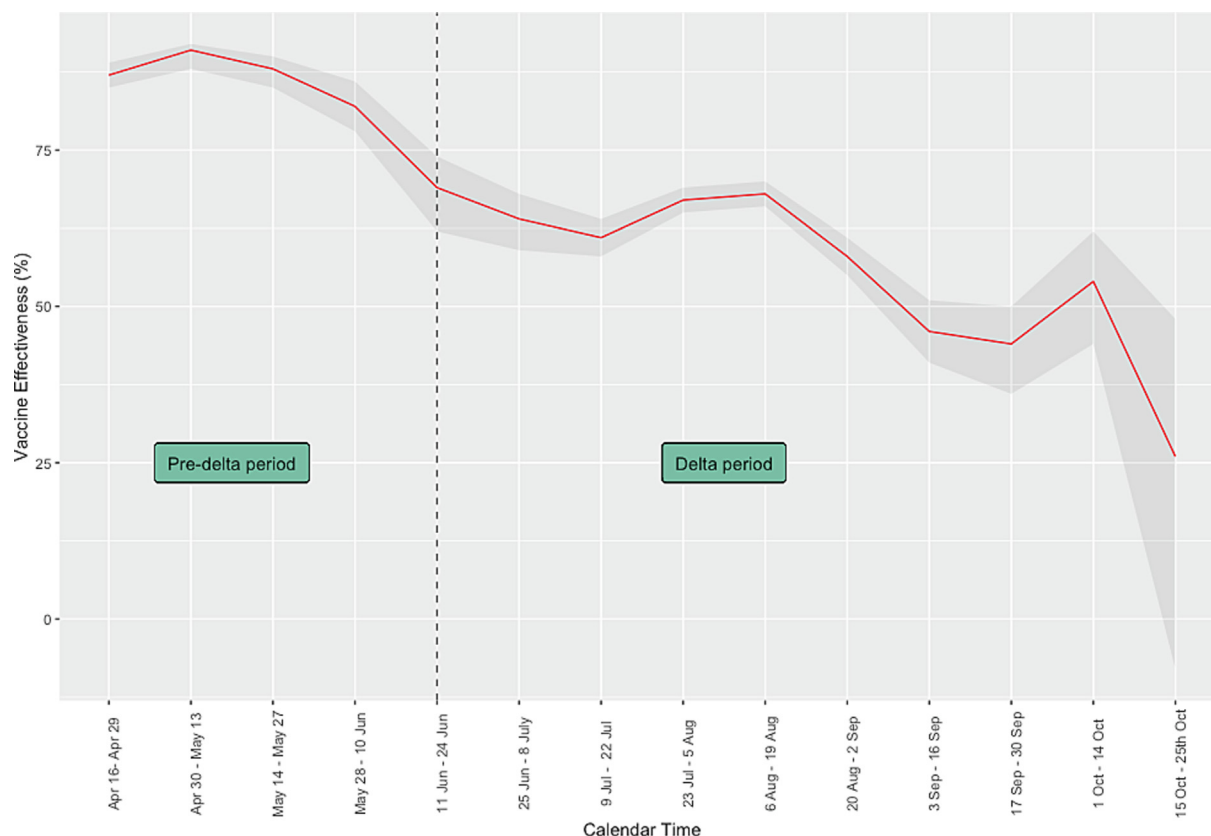
In sensitivity analyses, VE estimates against any SARS-CoV-2 infection detected by RT-PCR only and by both RT-PCR and antigen tests were consistent for both the 2-dose mRNA vaccines and the 1-dose Ad26.COV2.S vaccine (Supplementary Table 1).

#### 4. Discussion

Using a test-negative case-control study design, we estimated vaccine effectiveness against symptomatic and asymptomatic SARS-CoV-2 infection in a population of testers at urgent care centers in the NYC metropolitan area during the pre-delta and delta eras of the pandemic. We found that vaccine effectiveness after 2 doses of mRNA vaccines was very high (>90%) in the pre-delta period across subgroups of populations but declined over time. The mRNA-1273 vaccine was found to be slightly more effective compared to the BNT162b2 vaccine, while VE was much lower for recipients of the Ad26.COV2.S vaccine. Individuals with both prior infection and vaccination had the highest protection against infection. Comparisons between effectiveness of different vaccine products and between infection-induced, vaccine-induced, and hybrid protection can help inform policy decisions about boosters.

Because the study participants are restricted to those who attend an urgent care clinic for a test, the test-negative study design can potentially control for selection bias arising due to differences in healthcare-seeking behavior between cases and controls. Use of highly specific and sensitive molecular tests and highly specific rapid antigen tests for case detection makes outcome misclassification less likely [19,23]. This design has been popular for estimating COVID-19 vaccine effectiveness [24–26]. Our study contributes to a broader understanding of real-world COVID-19 vaccine effectiveness in key demographic groups. First, we estimated VE within population subgroups disproportionately affected by COVID-19, such as individuals >80 years, adolescents, Black and Hispanic adults, and those with comorbidities. Second, we were able to compare VE for all three FDA-approved and authorized vaccines in the US. Lastly, we compared infection-induced and vaccine-induced protection against both symptomatic and asymptomatic infections, addressing a key gap in COVID-19 vaccine effectiveness research.

Our estimates for VE against symptomatic infection for both partial and full vaccination with mRNA vaccines are comparable to findings of other studies performed in different settings and populations, especially for the pre-delta period [16,26–29]. Comparing the two mRNA vaccine products, we found higher VE estimates for the mRNA-1273 vaccine consistent with other studies



**Fig. 2.** Time-varying vaccine effectiveness against symptomatic and asymptomatic SARS-CoV-2 infections after 2-dose mRNA vaccines for patients testing in CityMD clinics between April 1, 2021 - October 25, 2021. The red line indicates vaccine effectiveness estimates for every 2-week interval during the study period and the 95% CI are shaded in grey. Both symptomatic and asymptomatic infections were included. The dashed horizontal line indicates the start of the Delta period. All estimates are adjusted for age, gender, race/ethnicity, region, testing prior to study period, and comorbidities. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

[17,30,31]. The difference in effectiveness between the two vaccines might be because of higher antigen dose in the mRNA-1273 vaccine or longer interval between doses [32]. The VE estimates for the Ad26.COV2.S vaccine were much lower compared to other published reports [25,33,34], particularly in the delta period. The reason for lower VE for the Ad26.COV2.S vaccine in general might be lower yields of antibody titres among Ad26.COV2.S vaccine recipients compared to mRNA vaccine recipients [35].

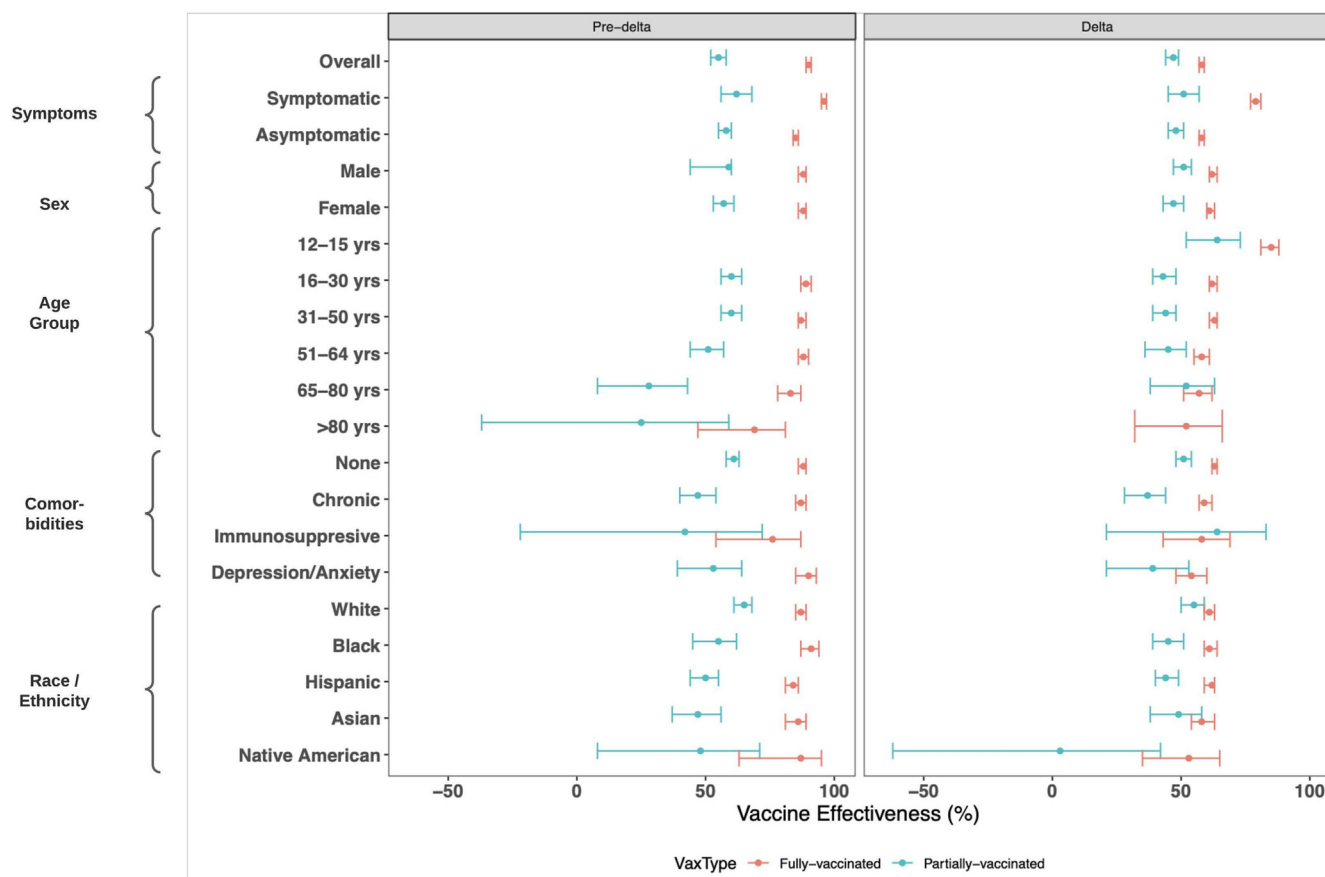
The stark drop in VE in early July is contemporaneous with the rise in prevalence of the Delta variant in New York City, which accounted for 60% of all cases by the end of June [36]. Some studies posit that decrease in VE is likely to be due to lower effectiveness against the delta variant [8,33], while others have attributed it to waning of vaccine effect [16,37]. As we did not have vaccination dates in our study, we could not directly differentiate between these two mechanisms. However, higher delta-period VE estimates for 12–15 year olds (who were vaccinated more recently) compared to VE estimates for 65+ year olds (who were vaccinated in early 2021) could suggest a possible waning effect. While mRNA vaccines have been moderately effective against Omicron, there is evidence of waning and new variants might emerge against which the current vaccines might not perform well. Given these uncertainties, it remains important to monitor how VE changes over time especially as new variants continue to emerge.

VE against infection among >65 year olds, as well as among those with comorbidities, had declined to under 60% by October 2021. These findings support CDC's recommendations to prioritize booster doses for these individuals, given their elevated risk of mortality and hospitalization [38]. Although VE was comparable

across race/ethnicities in our study, race alone might not fully capture socio-economic barriers to vaccination and healthcare such as health insurance status, health literacy, access to physicians, and social inequities that disproportionately affect communities of color. Gaps in vaccination coverage by race/ethnicity have narrowed as the pandemic has progressed, with a majority of unvaccinated people in the US now being White [39]. Reporting vaccine effectiveness estimates by social determinants of health in addition to race/ethnicity can help identify populations that can benefit the most from targeted vaccination strategies [40].

VE estimates comparing vaccine-induced and infection-induced protection from re-(infection) is scarce, complicated by the timing of vaccine roll-out in most populations less than a year into the pandemic. In line with other studies, we found that, in the pre-delta period, vaccine-induced and infection-induced protection were comparable for both mRNA vaccines, and vaccination following infection provided incremental protection against COVID-19 [41–43]. In the delta period, however, a history of infection was found to be more protective against re-infections compared to vaccination without prior infection, similar to evidence found in Israel and India [44,45], but in contrast to evidence from the US [46]. In our study, the relatively short average time since previous infection (4 months) could be the reason for higher protection among those with prior infection [43,47].

Individuals with previous infection and one dose of the either mRNA vaccine had high protection against re-infection, suggesting that the first dose of the mRNA vaccine may act like a booster for those who were previously infected [48]. Even so, full vaccination including boosters is still highly recommended for those with prior



**Fig. 3.** Estimated vaccine effectiveness after 2-dose mRNA vaccines against symptomatic and asymptomatic SARS-CoV-2 infection in different population subgroups mRNA vaccine effectiveness and 95% confidence intervals after 2 doses (red) and 1 dose (blue) of the vaccine for different population subgroups in pre-delta (left panel) and delta (right panel) periods are displayed here. Both symptomatic and asymptomatic SARS-CoV-2 cases were included for the overall VE estimates and the VE estimates by subgroups. Patients 12–15 years old became eligible for COVID-19 vaccination on May 12, 2021 so vaccination information for this age group was available for the pre-delta period. For those who were partially vaccinated, it is not known if the dose was given 2 weeks prior to when the diagnostic test was conducted. Estimates are adjusted for age, gender, race/ethnicity, region, testing prior to study period, and comorbidities, as applicable. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

infection, because levels of protection can vary based on age and disease severity [49], while VE is relatively uniform across populations, with the possible exception of older and immunocompromised individuals [50]. Furthermore, even mild disease can lead to long COVID-19 [51].

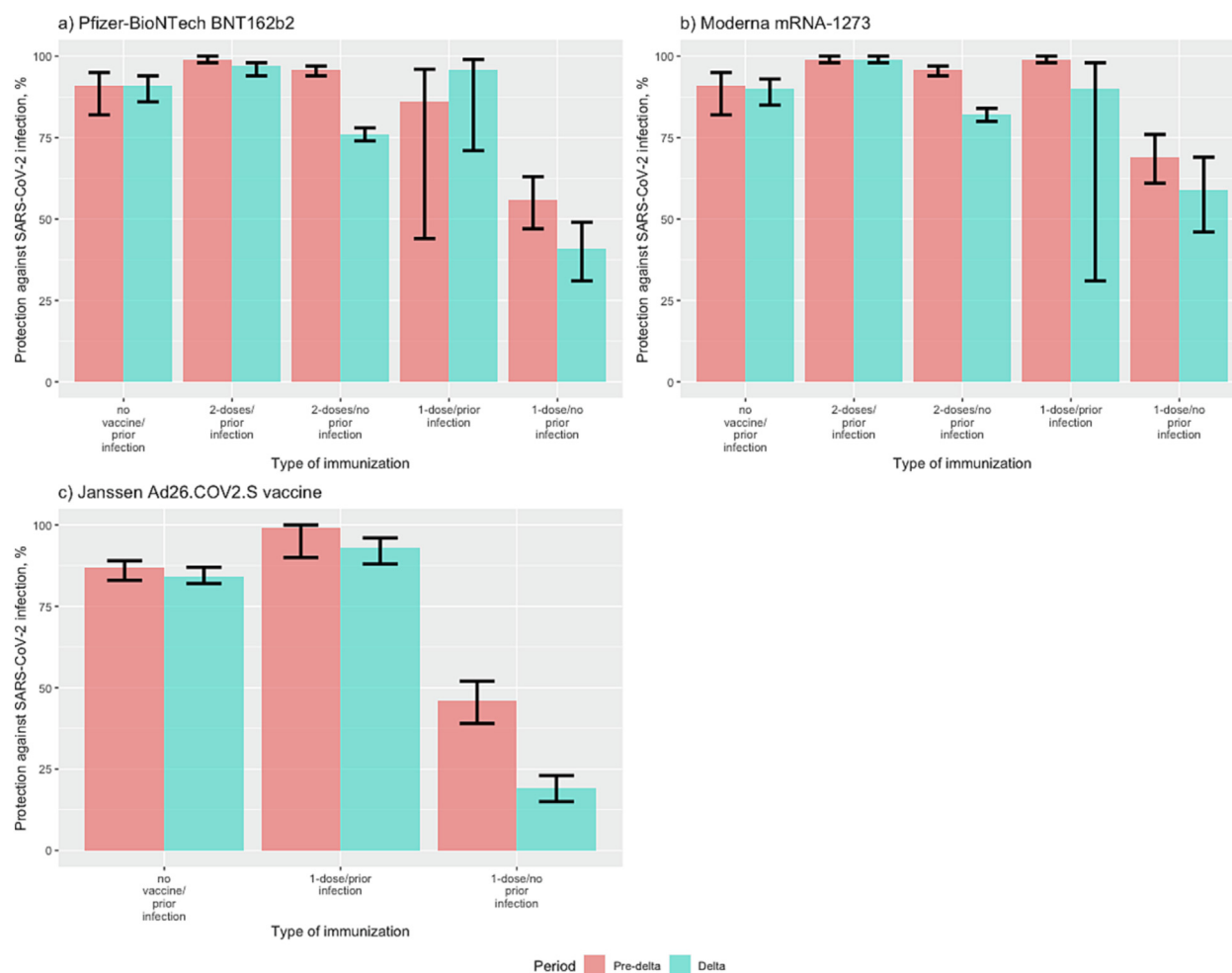
Our study has limitations. Even though test-negative design controls for bias due to healthcare-seeking behavior and access, the rates of testing between vaccinated and unvaccinated people might differ. Vaccinated individuals with symptoms could be more motivated to get tested which would lead to an overrepresentation of vaccinated individuals with positive test results, biasing the VE estimates downwards. Bias due to unmeasured confounders, such as occupation or behavior changes following policies or vaccination is also possible [52]. We may have missed reports of prior infections if participants were tested at other clinics, which could also bias VE estimates downwards. Outcomes for the patients who received only an antigen test could be misclassified due to lower test sensitivity. However, our sensitivity analysis showed that when restricted to the highly sensitive RT-PCR tests results, VE estimates were nearly identical to those of the overall sample. Misclassification of exposure is a possibility as vaccination status was

self-reported and dates of vaccination were not collected. However, other studies have shown high agreement between self-reported and recorded COVID-19 vaccination status [53,54–56]. VE after one dose of mRNA vaccines is likely underestimated in this study because it was not known if the outcome occurred >15 days after the first dose. We did not collect information on disease severity and hospitalization and could not differentiate between asymptomatic and pre-symptomatic patients. These results are not generalizable to populations that do not seek healthcare at ambulatory clinics in NYC.

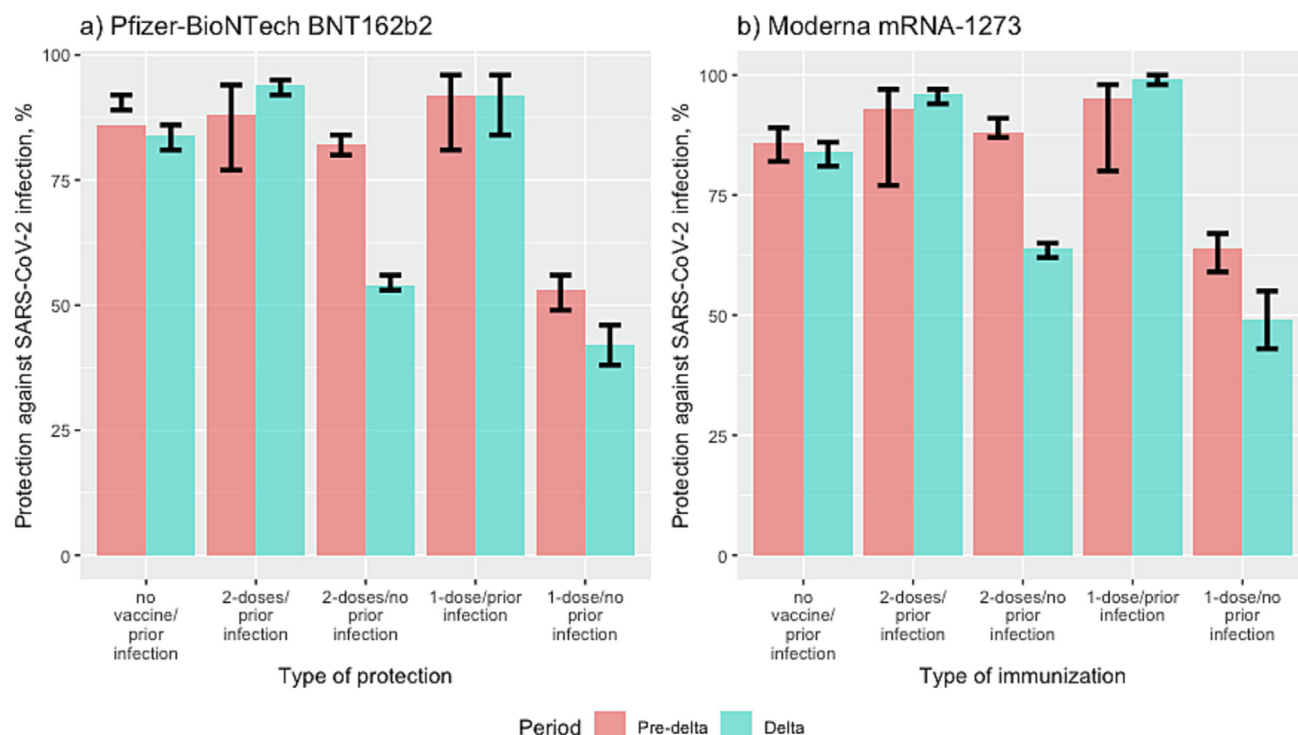
In conclusion, our analysis of urgent care visit data over a 7-month period showed high overall effectiveness after two doses of the mRNA vaccine in the pre-delta period, but significantly reduced vaccine effectiveness against the delta variant for all three FDA-approved vaccines. Prior infection combined with full vaccination provided high protection regardless of which variant was predominant. Our findings support continued monitoring of vaccine effectiveness by vaccine product as new variants emerge.

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**Fig. 4.** Estimated vaccine-induced and infection-induced protection against *symptomatic* SARS-CoV-2 infection by vaccine product Bar graph shows protection and 95% confidence intervals against SARS-CoV-2 symptomatic infection comparing patients with infection-induced protection, vaccine-induced protection, or both, to patients who were unvaccinated (no vaccine-induced protection) and had no prior infections (no infection-induced protection). Results are shown separately for the (a) Pfizer-BioNTech BNT 162b2 vaccine, (b) Moderna mRNA-1273 vaccine, and (c) Janssen Ad26.COV2.S vaccine. Moderna vaccine 2-dose/prior infection (pre-delta and delta periods) and Janssen vaccine 1-dose/prior infection (pre-delta period) groups had 0 cases, so 0.5 added to the cell to obtain lower bounds of the confidence interval. Protection during pre-delta period is in red while protection during delta period is in blue. For those who were partially vaccinated, it is not known if the dose was given 2 weeks prior to when the diagnostic test was conducted. All estimates are adjusted for age, gender, race/ethnicity, region, testing prior to study period, and comorbidities. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)



**Fig. 5. Estimated vaccine-induced and infection-induced protection against asymptomatic SARS-CoV-2 infection by vaccine product** Bar graph shows protection and 95% confidence intervals against SARS-CoV-2 asymptomatic infection comparing patients with infection-induced protection, vaccine-induced protection, or both, to patients who were unvaccinated (no vaccine-induced protection) and had no prior infections (no infection-induced protection). Moderna vaccine 1-dose/prior infection group had 0 cases, so 0.5 added to the cell to obtain lower bounds of the confidence interval. Results are shown separately for the (a) Pfizer-BioNTech BNT 162b2 vaccine, and (b) Moderna mRNA-1273 vaccine. None of the patients with asymptomatic infections received the Janssen Ad26.COV2.S vaccine, hence no data is available for VE of Ad26.COV2.S vaccine against asymptomatic infection. Protection during pre-delta period is in red while protection during delta period is in blue. For those who were partially vaccinated, it is not known if the dose was given 2 weeks prior to when the diagnostic test was conducted. All estimates are adjusted for age, gender, race/ethnicity, region, testing prior to study period, and comorbidities. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

## Data availability

The authors do not have permission to share data.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2022.12.039>.

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